

terms of activity of anti-Xa per milligram), which are more selective with respect to anti-Xa activity than that of heparin and have a lower whole anticoagulation activity than heparin (measured in USP units per milligram), which heparinic mucopolysaccharide fractions have (1) a molecular weight in the range of about 2,000 to 10,000 daltons, (2) are soluble in water-alcohol having a titer of 55-61°GL, (3) are insoluble in alcohol, (4) have a ratio of anti-Xa titer to USP titer of at least 3, wherein in said heparinic mucopolysaccharides, fractions comprise (5) glucosamine units which are sulfated in the primary position, (6) one N-acetyl glucosamine unit for two 2-O-sulfate iduronic acid units and for two N-sulfate-glucosamine units, and the pharmaceutically acceptable salts thereof.

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109. The mucopolysaccharides of claim 108, the carbon-13 NMR spectrum of which exhibits glucosamine units, the primary carbons in the 6-position being free of hydroxyl group and exhibiting resonance signals in the region corresponding to chemical displacements in the 100 ppm region (as shown by stars in Fig. 14).

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110. The mucopolysaccharides of claim 109, wherein the carbon-13 NMR spectrum exhibits another resonance signal in the 75 ppm region.

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111. The mucopolysaccharides of claim 110, wherein the proton NMR spectrum exhibits resonance signals in the 4.8, 5.2 and 5.4 ppm regions, which signals in the 4.8 and 5.2 ppm regions being weaker than that in the 5.4 ppm region.

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112. The mucopolysaccharides of claim 109, wherein the carbon-13 NMR spectrum exhibits a supplementary signal in the 60 ppm region adjoining the G_2 designated signal (as shown in Fig. 14).

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113. The mucopolysaccharides of claim 108, which is shown by one of the NMR spectra of Figs. 11, 12, 14 or 15.

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114. The mucopolysaccharides of claim 109, which have a USP titer of about 45 units per mg, an anti-Xa factor titer of about 160 units per mg and a ratio of anti-Xa titer to USP titer of about 3.55.

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115. The mucopolysaccharides of claim 114, wherein the USP titer is less than about 10 units per mg.

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116. The mucopolysaccharides of claim 109, wherein the ratio of anti-Xa titer to USP titer is at least 6.

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117. The mucopolysaccharides of claim 116, wherein the ratio of anti-Xa titer to USP titer is at least 10.

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118. The mucopolysaccharides of claim 117, wherein the ratio of anti-Xa titer to USP titer is at least 50.

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119. The mucopolysaccharides of claim 118, wherein the ratio of anti-Xa titer to USP titer is at least 130.

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120. The mucopolysaccharides of claim 116, wherein
the anti-Xa titer is not less than about 50 units per mg.

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121. The mucopolysaccharides of claim 120, wherein
the anti-Xa titer is at least 300 units per mg.

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122. The mucopolysaccharides of claim 121, wherein
the anti-Xa titer is at least 900 units per mg.

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123. The mucopolysaccharides of claims 108, 124, 125,
116 or 120, wherein the molecular weights are in the range of
about 2,000 to about 8,000 daltons.

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124. The mucopolysaccharides of claim 108, wherein
the USP titer does not exceed about 13 units per mg, the
anti-Xa titer is in the range of about 135 to about 160 units
per mg, the ratio of anti-Xa units to USP units is in the range
of 13 to 16 and the molecular range is from about 4,000 to
about 8,000 daltons.

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125. The mucopolysaccharides of claim 108, wherein
the USP titer does not exceed about 6 units per mg, the anti-Xa
titer is not less than about 44 units per mg, the ratio of
anti-Xa to USP titers is over about 9 and the molecular weight
is in the range of about 4,000 to 8,000 daltons.

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126. The mucopolysaccharides of claim 108, wherein
the salts are selected from the group consisting of sodium and
calcium.

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121. The mucopolysaccharides of claim 108, which are selectively fixable on antithrombin III.

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128. A therapeutic composition which comprises a therapeutically acceptable carrier and in an antithrombotic effective amount, the heparinic mucopolysaccharide fractions of claims 108, 109, 110, 111, 112, 113, 114, 115, 116, 117, 118, 119, 120, 121, 122, 123, 124, 125, 126 or 127.

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129. The therapeutic composition of claim 128 which has an anti-Xa titer higher than about 100 units per mg.

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130. The therapeutic composition of claim 128, which is a solution of the mucopolysaccharides in a concentration of about 1,000 to 100,000 Yin-Wessler units per ml.

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131. The therapeutic composition of claim 130 which is a solution of the mucopolysaccharides in a concentration of about 5,000 to about 50,000 units per ml.

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132. A therapeutic method for controlling thrombosis in a patient which comprises administering to the patient in a therapeutically antithrombotic effective amount, the composition of claims 128, 129, 130 or 131 and controlling thrombosis by inhibiting coagulation factor Xa.

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133. The therapeutic method of claim 132 wherein the administration of the composition is by injection or infusion.

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134. A process for obtaining heparinic mucopolysaccharides which have improved antithrombotic activity

in vivo and inhibition of the Xa-factor (measured in terms of anti-Xa activity) more selective than that of heparin and a lower whole anticoagulation activity than heparin (measured in USP units), which mucopolysaccharides have a molecular weight in the range of about 2,000 to 10,000 daltons, a ratio of anti-Xa to USP titers of at least 3, which process comprises mixing heparin mucopolysaccharides having a molecular weight in the range of about 2,000 to 50,000 daltons in a 55-61°GL aqueous-alcoholic medium, separating the liquid medium which contains mucopolysaccharides in solution and precipitating out the soluble mucopolysaccharides by alcoholic precipitation, said mucopolysaccharides having an increased ratio of anti-Xa titer to USP titer as compared to the starting heparin mucopolysaccharides.

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135. The process of claim *134*, which comprises recovering the alcohol-precipitated mucopolysaccharides, subjecting an aqueous solution of said mucopolysaccharides to gel-filtration and recovering the fraction, which fraction has a further increased anti-Xa titer to USP titer ratio as compared to that of the alcohol-precipitated mucopolysaccharides.

28.3
28.1 *28.2*
136. The process of claims *134* or *135*, which comprises the further step of contacting the mucopolysaccharides which have increased anti-Xa titer with antithrombin III, selectively affixing thereon the mucopolysaccharides which have a higher Yin-Wessler activity than the mucopolysaccharides which are not affixed thereon and recovering the affixed mucopolysaccharides by elution, which mucopolysaccharides have further increased anti-Xa titer to USP titer ratio than the starting mucopolysaccharides. *—*